CONTINUOUS CARDIAC PERFUSION PRESERVATION WITH PEG-HB FOR IMPROVED HYPOTHERMIC STORAGE

Be it known that we, Danny L. Serna Jr., Jeffrey C. Milliken, and Ralph E. Purdy, each citizens of the United States, have invented a new and useful method and apparatus for continuous cardiac perfusion preservation with PEG-Hb for improved hypothermic storage of which the following is a specification.

Donor organ preservation for transplantation is performed using ischemic hypothermic immersion storage in saline solution. Preservation time for the donor cardiac allograft, for example, is limited to a maximum of 4 to 6 hours using this technique. Hypothermic perfusion preservation with an oxygen carrying hemoglobin solution should extend preservation times and decrease ischemic injury of transplantable organs. Perfusion preservation using the invention will also allow sufficient time for complex tissue typing, allow better donor-recipient matching, and allow for transportation of organs to more distant sites.

Prior art bearing on the invention includes PEG-Hb which Enzon, Inc as described in U.S. Patent 5,312,808. The invention differs from prior art in terms of the composition of the solution. The invention contains PEG-Hb as one of numerous components. In addition to PEG-Hb, the invention contains human albumin, dextrose, heparin sodium, lidocaine HCl, $MgSO_4$, KCl, $CaCl_2$, THAM, NaCl, NaHCO3, Na_3P0_4, without which PEG-Hb is lethal to the myocardium and cannot be used for the purpose of effective organ preservation.

In the past, the problem of cardiac allograft preservation was accomplished by hypothermic immersion storage of the allograft in cardioplegia or saline solution. The disadvantage of this technique was the lack of delivery of oxygen, nutrition, and electrolytes to the donor organ allograft. Use of PEG-Hb alone is lethal to the myocardium and cannot be used for the purpose of effective organ preservation. An electrolyte and nutritional formulation was developed that included PEG-Hb and was found to improve and extend myocardial preservation times above that achieved by standard techniques.

The invention includes a composition of matter, namely a polyethylene glycol coated bovine hemoglobin based solution for the purpose of ex vivo donor

organ preservation and the use of the same. The purpose of the solution is to preserve donor human and animal organs, *ex vivo*, prior to transplantation. The fundamental principle of the solution is to provide an oxygen, nutritional and electrolyte environment to the tissue of the donor organ that is conducive to *ex vivo* preservation such that the donor organ will regain acceptable function post transplantation.

The invention is a product, composition, and method of use and is set forth in greater specificity in Appendices 1 – 3 which are incorporated herein by reference as if set out in its entirety with Appendix 3 being the most current implementation of the invention.

The advantages of the invention include provision of oxygen, a carbohydrate energy source, continuous metabolite washout, and continuous perfusion with an isotonic, normokalemic, hypocalcemic solution that drastically improves myocardial preservation over current techniques considered the standard of care. Hypothermic perfusion preservation of the rabbit heart using the invention for periods of 8 hours has been shown to improve myocardial preservation and left ventricular function compared to 4 hours of hypothermic immersion storage in saline solution, which is considered to be the standard of care. Hypothermic perfusion preservation of the rabbit heart using the invention for periods of 8 hours has also been shown to produce left ventricular function that trends toward superiority over fresh control rabbit hearts immediately after removal from the chest.

The illustrated composition of the PEG-Hb based preservation fluids is as follows: 3% PEG-Hb, KCL (4.7 mEq/L), NaCl (148.7 mmol/L), NaPO4 (2.5 mmol/L), NaHCO3 (2.5 mmol/L), $MgSO_4$ (5.0 mEq/L), $CaCl_2$ (1.0 mEq/L), lidocaine HCl (12.5 mg/L), heparin sodium (1250 units/L), dextrose (6.1 mOsm/L), human albumin (1.5 gm/L), human insulin (30.6units/L), Tromethamine (THAM) solution (7.3 cc/L).

The composition of the crystalloid preservation solution is as follows: KCL (4.7 mEq/L), NaCl (150.7 mEq/L), $MgSO_4$ (5.0 mEq/L), $CaCl_2$ (1.0 mEq/L), lidocaine HCl (12.5 mg/L), heparin sodium (1250 units/L), dextrose (6.1 mOsm/L),

human albumin (1.5 gm/L), human insulin (30.6 units/L), and Tromethamine (THAM) solution (7.3 cc/L).

During *ex vivo* cardiac preservation, the pH of the invention is maintained at 7.1, as measured at 37°C, and 7.4 as measured at 20°C. The pO2 is maintained above 600 mm Hg. New Zealand White rabbits were used to obtain data to support this disclosure.

The proposed use of the invention is for the *ex vivo* preservation of human and animal donor organ allografts during transportation from the donor to the recipient for the purpose of transplantation. In addition to its use for ex vivo myocardial preservation, this PEG-Hb solution has tremendous potential utility for in vivo myocardial preservation during open heart surgery as well as a blood substitute or blood replacement during or following surgery of any sort, including open heart surgery.

By increasing the potassium concentration of the solution to reflect intracellular levels, this solution could very well be useful for the purposes of cardioplegia or hypothermic cardiac arrest as well as myocardial preservation during open-heart surgery. The solution could be administered in order to effect and maintain myocardial arrest as well as improve myocardial preservation during open heart surgery.

The current formulation of the PEG-Hb solution would likely be extremely effective for the purposes of intravascular volume replacement, blood substitution, and as an alternative to blood transfusion during or after surgery of any sort including, but not limited to open heart surgery, and including trauma induced blood loss.

Many alterations and modifications may be made by those having ordinary skill in the art without departing from the spirit and scope of the invention. Therefore, it must be understood that the illustrated embodiment has been set forth only for the purposes of example and that it should not be taken as limiting the invention which could be more broadly or narrowly defined later by patent claims.

The words used in this specification to describe the invention and its various embodiments are to be understood not only in the sense of their

commonly defined meanings, but to include by special definition in this specification structure, material or acts beyond the scope of the commonly defined meanings. Thus if an element can be understood in the context of this specification as including more than one meaning, then its use in later in a claim must be understood as being generic to all possible meanings supported by the specification and by the word itself.

The definitions of the words or elements of the following claims are, therefore, defined in this specification to include not only the combination of elements which are literally set forth, but all equivalent structure, material or acts for performing substantially the same function in substantially the same way to obtain substantially the same result. In this sense it is therefore contemplated that an equivalent substitution of two or more elements may be made for any one of the elements in later defined claims or that a single element may be substituted for two or more elements in later defined claims.

Insubstantial changes from the claimed subject matter as viewed by a person with ordinary skill in the art, now known or later devised, are expressly contemplated as being equivalently within the scope of the invention. Therefore, obvious substitutions now or later known to one with ordinary skill in the art are defined to be within the scope of the defined elements.

The invention is thus to be understood to include what is specifically illustrated and described above, what is conceptionally equivalent, what can be obviously substituted and also what essentially incorporates the essential idea of the invention.